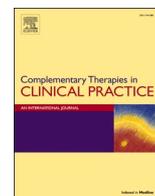




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Herbal medicine for treatment of children diagnosed with COVID-19: A review of guidelines

Lin Ang^{a,b,1}, Hye Won Lee^{c,1}, Anna Kim^d, Ju Ah Lee^e, Junhua Zhang^f, Myeong Soo Lee^{a,b,f,*}

^a Clinical Medicine Division, Korea Institute of Oriental Medicine, Daejeon, South Korea

^b Korean Convergence Medicine, University of Science and Technology, Daejeon, South Korea

^c Herbal Medicine Research Division, Korea Institute of Oriental Medicine, Daejeon, South Korea

^d Future Medicine Division, Korea Institute of Oriental Medicine, Daejeon, South Korea

^e Hwa-pyeong Institute of Integrative Medicine, Incheon, South Korea

^f Evidence-based Medicine Centre, Tianjin University of Traditional Chinese Medicine, Tianjin, China

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ABSTRACT

This review aimed to summarize and analyze the pattern identification (PI), herbal formulae, and composition of herbs provided by recent guidelines for the treatment of pediatric COVID-19. Seven data sources were reviewed until March 25, 2020. We analyzed the herbal formulae included in the guidelines and performed a network analysis to identify the frequency of herbs recommended in the herbal formulae. All 3 guidelines were provincial guidelines from China. Our results showed that there were 4 stages, 12 PIs, and 13 herbal formulae recommended by the provincial guidelines. These herbal formulae included a total of 56 herbs. Based on our network analysis, *Scutellariae Radix* was paired with *Artemisiae Annuae Herba* in one cluster. In another cluster, *Armeniacae Semen* was paired with *Coicis Semen* and *Ephedrae Herba* was paired with *Gypsum Fibrosum*. This review serves as a reference for the use of traditional medicine in the treatment of pediatric COVID-19.

1. Introduction

As of March 2020, the outbreak of coronavirus disease (COVID-19) has been declared a pandemic, and at least 163 countries across all six continents sustained the transmission of the virus [1,2]. Although there is very limited information about the virus, current evidences show that people can be ill from COVID-19 regardless of their age, gender, ethnicity, and health status. While children are less likely to be infected by the virus as compared to the adults, they are not spared from the disease.

Recent epidemiological reports also showed that the cases reported among children are relatively few and less severe [3]. Mainland China, which has the highest number of cases worldwide has reported that the mean age of pediatric patients with COVID-19 infection was 7 years old. According to the Chinese Center for Disease Control and Prevention (China CDC), there are no fatalities found in children with age ranging from 1 to 9 years old [4]. Regardless of the number of cases reported, children remain vulnerable to COVID-19.

As there is no vaccine or antiviral treatment currently available for

COVID-19, traditional medicine, which has been widely used in the past during epidemic outbreaks, is taken into consideration as one of the treatment modalities [5]. Although many countries have issued traditional medicine treatment guidelines on the prevention and treatment of COVID-19, only mainland China has issued the guidelines for children.

This review aimed to systematically summarize and analyze the herbal formulae recommended by all available Chinese guidelines in terms of the composition of herbs, pattern identification (PI) and disease stages in the treatment of pediatric COVID-19.

2. Methods

2.1. Data sources

Seven data sources were searched, until March 25, 2020, to identify available traditional medicine guidelines:

- Guidelines International Network (G-I-N) [6].

* Corresponding author. Clinical Medicine Division, Korea Institute of Oriental Medicine, Daejeon, 34054, South Korea.

E-mail addresses: mslee@kiom.re.kr, drmslee@gmail.com (M.S. Lee).

¹ Both authors contributed equally to this work.

- “Chinese guidelines on Novel Coronavirus” resource by Evidence Aid [7].
- The official government websites of all 31 provinces in Mainland China (including municipal and autonomous regions)
- The Centre for Health Protection of the Hong Kong Special Administrative Region [8].
- Association of Korean Medicine and Korean Association of Traditional Pulmonary Medicine
- Japanese Association for Infectious Diseases and Japanese Respiratory Society [9].
- Taiwan Centers for Disease Control [10].

2.2. Inclusion and exclusion criteria

This study focused on the recommended treatment modalities in traditional medicine for pediatric COVID-19. All herbal formulae recommended by the guidelines for treatment measures were included and those for preventive measures were excluded.

As herbal formulae provided by guidelines from the different provinces were formulated based on regional characteristics, regional folk medicines such as Tibetan medicine, Mongolian medicine, and Miao medicine were excluded. For provincial guidelines that integrate both folk medicine and conventional traditional medicine, only herbal formulae of the latter were included.

2.3. Data extraction and analyses

Data from the included guidelines were extracted based on a pre-defined data extraction table which included the stages of the disease, pattern identification, clinical symptoms, therapeutic principle, name and composition of herbal formulae, herb dosage, and the province of the provided guideline. The herbal formulae were analyzed based on pattern identification and disease stage. The frequency of herbs recommended in the herbal formulae were also identified by performing a network analysis using Netminer 4.0 (Cyram Inc, Seoul, Korea) which visualized the relationship between the herbs in clusters. In our network analysis, the nodes represented the herbs and their connections represented the relationship of the herbs with each other. The connections were stronger in herbs that were adjacent to each other. The herbs with closer connection as compared to the rest of the network belonged to the same cluster.

2.4. Terminology standardization

We standardized all the terminologies based on the *WHO International Standard Terminologies on Traditional Medicine in Western Pacific Region* [11]. Pattern identification terminology was standardized based on the clinical manifestation provided in the guidelines and *Clinic Terminology of Traditional Chinese Medical Diagnosis and Treatment* [12]. Unnamed herbal formulae were renamed using the *Dictionary of Traditional Chinese Medicine Formula* [13].

3. Results

We only found 3 traditional medicine guidelines from mainland China that provide treatment measures for pediatric COVID-19. Although there were several versions of national diagnosis and treatment guidelines related to traditional medicine issued in mainland China, contents on pediatric treatments were not provided in any of these guidelines. All 3 traditional medicine guidelines included in this review were issued by the provincial government.

The herbal formulae used for treating children diagnosed with COVID 19 were analyzed based on the disease stages and PI. Our results identified 4 stages and 12 PIs based on the provided provincial guidelines. There were 13 herbal formulae recommended by the provincial guidelines, of which 12 herbal formulae were oral decoction

prescriptions and one of them was a decoction enema prescription (Table 1). The frequency of the herbs used in the herbal formulae was also calculated. These herbal formulae included a total of 56 herbs, of which 23 had a frequency of use of 3 or more times.

In the results of our network analysis, 11 herbs that appeared more than 3 times in the herbal formulae were able to be classified into two different clusters (Fig. 1), where 6 herbs (*Angelicae Decursivae Radix*, *Belamcandae Rhizoma*, *Eriobotryae Folium*, *Trichosanthis Pericarpium*, *Scutellariae Radix*, and *Artemisiae Annuae Herba*) belonged to one cluster and the other 5 (*Armeniacae Semen*, *Lepidii seu Descurainiae Semen*, *Coicis Semen*, *Gypsum Fibrosum*, and *Ephedrae Herba*) belonged to the second cluster. In the figure, *Scutellariae Radix* showed strong connections with *Artemisiae Annuae Herba* and *Belamcandae Rhizoma* in one cluster. The herb *Armeniacae Semen* and *Coicis Semen*, in addition to *Ephedrae Herba* and *Gypsum Fibrosum*, each had strong connections with one another in the other cluster.

4. Discussion

In this review, we systematically accessed the herbal treatment recommended by the Chinese provincial guidelines for pediatric COVID-19. According to our results, only 3 provincial guidelines provided herbal treatment recommendations for pediatric COVID-19. A recent case series of 72,314 cases published by the Chinese Center for Disease Control and Prevention showed that children younger than 10 years old accounted for only 1% of cases and another 1% were patients whose age ranged from 10 to 19 years [4]. Besides, recent evaluation of the pediatric cases treated at the Wuhan Children’s Hospital, which is the only hospital in Wuhan, China that was assigned by the government for the treatment of pediatric COVID-19, also reported that most infected children presented with milder symptoms as compared to adults [3]. This may be the rationale behind the lack of guidelines issued for the treatment of pediatric COVID-19.

According to our network analysis, *Scutellariae Radix*, *Artemisiae Annuae Herba*, and *Belamcandae Rhizoma* were found to be correlated in one cluster. In the theory of traditional medicine, these three herbs have a heat-clearing effect and are frequently used together in herbal formulae. The herb *Scutellariae Radix* is approved by the China Food and Drug Administration for the treatment of viral diseases such as influenza, upper respiratory infection, and pneumonia [14]. *Baicalin*, which is the main bioactive compound derived from *Scutellariae Radix*, was also reported to have antiviral activity against SARS coronavirus [15]. Similarly, *Artemisiae Annuae Herba* was reported to have an antiviral compound and showed inhibitory effects on the SARS coronavirus strain [16]. Besides, *Belamcandae Rhizoma* has also been frequently used for the treatment of inflammation and throat disorder [17].

Additionally, our results also showed that *Armeniacae Semen* and *Coicis Semen* were correlated to one another in the second cluster. The herb *Armeniacae Semen* and *Coicis Semen* were often prescribed together for the treatment of upper respiratory infection as they both have the effect of nourishing the lungs in traditional medicine [18]. The herb *Ephedrae Herba* and *Gypsum Fibrosum* were also shown to have strong connections with one another. Both herbs are the major components of the herbal formula *Ma Xin Shi Gan Tang*, which is often used for the treatment of common cold. This herbal formula also claimed to antiviral effect that inhibits the entry of influenza virus and have potential in managing seasonal pandemics of influenza infection [19].

Notably, the herb *Armeniacae Semen* was one of the highest frequencies of use among the herbal formulae recommended for the treatment of pediatric COVID-19. In a nationwide population-based study conducted in Taiwan, *Armeniacae Semen* was the most frequently prescribed herb for the treatment of pediatric asthma [20]. Besides having antiasthmatic activity, *Armeniacae Semen* was also reported to inhibit Th₂ cells, which are important for immune responses, reducing hyper-responsiveness in the airway [21]. This further validated

Table 1
Pattern identification and herbal medicines recommendation for pediatric COVID-19.

Stages	Pattern Identification	Name of herbal formula	Composition of herbal formula
Mild	Seasonal Epidemic Invading the Exterior-defense	Yin Qiao San	△ <i>Lonicerae Flos</i> , <i>Forsythiae Fructus</i> , <i>Platycodonis Radix</i> , <i>Menthae Herba</i> , <i>Lophatheri Herba</i> , <i>Schizonepetae Spica</i> , <i>Glycine Semen Preparatum</i> , <i>Arctii Semen</i> , <i>Phragmitis Rhizoma</i> , <i>Cyperis Rhizoma</i> , <i>Perillae Folium</i> , <i>Citri Reticulatae Pericarpium</i> , <i>Glycyrrhizae Radix et Rhizoma</i> , <i>Bupleuri Radix</i> , <i>Cinnamomi Ramulus</i> , <i>Saposhnikoviae Radix</i> , <i>Osterici seu Notopterygii Radix et Rhizoma</i>
		Xiang Su San	△ <i>Ephedrae Herba</i> , <i>Armeniacae Semen Amarum</i> , <i>Glycyrrhizae Radix et Rhizoma</i> , <i>Gypsum Fibrosum</i> , <i>Amomi Fructus Rotundus</i> , <i>Coicis Semen</i> , <i>Pinelliae Rhizoma Praeparatum</i> , <i>Magnoliae Cortex</i> , <i>Talcum</i> , <i>Stachyuri Medulla Helwingiae Medulla</i> , <i>Lophatheri Herba</i>
Moderate	Dampness-Heat Blocking the Lung	Ma Xing Shi Gan Tang + San Ren Tang	△ <i>Citri Reticulatae Pericarpium</i> , <i>Atractylodis Rhizoma</i> , <i>Magnoliae Cortex</i> , <i>Glycyrrhizae Radix et Rhizoma</i> , <i>Amomi Tsao-ko Fructus</i> , <i>Pinelliae Rhizoma</i> , <i>Agastachis Herba</i>
		Buhuan Jin Zhengqi San	△ <i>Gypsum Fibrosum</i> , <i>Rhei Radix et Rhizoma</i> , <i>Armeniacae Semen Amarum</i> , <i>Trichosanthis Fructus</i> , <i>Talcum</i> , <i>Scutellariae Radix</i> , <i>Artemisiae Scopariae Herba</i> , <i>Acori Tatarinowii Rhizoma</i> , <i>Fritillariae Cirrhosae Bulbus</i> , <i>Akebiae Caulis</i> , <i>Agastachis Herba</i> , <i>Forsythiae Fructus</i> , <i>Amomi Fructus Rotundus</i> , <i>Menthae Herba</i> , <i>Belamcandae Rhizoma</i>
Severe	Heat Toxin Blocking the Lung	Xuanbai Chengqi Tang + Ganlu Xiaodu Dan	△ <i>Gypsum Fibrosum</i> , <i>Rhei Radix et Rhizoma</i> , <i>Armeniacae Semen Amarum</i> , <i>Trichosanthis Fructus</i> , <i>Talcum</i> , <i>Scutellariae Radix</i> , <i>Artemisiae Scopariae Herba</i> , <i>Acori Tatarinowii Rhizoma</i> , <i>Fritillariae Cirrhosae Bulbus</i> , <i>Akebiae Caulis</i> , <i>Agastachis Herba</i> , <i>Forsythiae Fructus</i> , <i>Amomi Fructus Rotundus</i> , <i>Menthae Herba</i> , <i>Belamcandae Rhizoma</i>
		Not available	<i>Rhei Radix et Rhizoma</i> (Enema using herbal decoction)
Recovered	Intense Heat Toxin with Blockage of Bowel Qi and Dysphagia Unclear Residual Heat	Liu Junzi Tang + Yu Ping Feng San	△ <i>Ginseng Radix</i> , <i>Atractylodis Macrocephalae Rhizoma</i> , <i>Poria Sclerotium</i> , <i>Glycyrrhizae Radix et Rhizoma</i> , <i>Citri Reticulatae Pericarpium</i> , <i>Pinelliae Rhizoma</i> , <i>Saposhnikoviae Radix</i> , <i>Astragali Radix</i>
		Not reported	<i>Ephedrae Herba</i> 4 g, <i>Gypsum Fibrosum</i> 20 g, <i>Anemarrhenae Rhizoma</i> 9 g, <i>Armeniacae Semen Amarum</i> 10 g, <i>Coicis Semen</i> 10 g, <i>Phragmitis Rhizoma</i> 10 g, <i>Platycodonis Radix</i> 6 g, <i>Mori Radicis Cortex</i> 10 g, <i>Lonicerae Flos</i> 10 g
Not reported	Heat Toxin Fettering the Lung	Ma Xing Shi Gan Tang*	<i>Ephedrae Herba</i> 4 g, <i>Gypsum Fibrosum</i> 20 g, <i>Anemarrhenae Rhizoma</i> 9 g, <i>Armeniacae Semen Amarum</i> 10 g, <i>Coicis Semen</i> 10 g, <i>Trichosanthis Fructus</i> 10 g, <i>Rhei Radix et Rhizoma</i> 5 g, <i>Mori Radicis Cortex</i> 10 g, <i>Lepidii seu Descurainiae Semen</i> 6 g, <i>Bubali Cornu</i> 10 g, <i>Pheretima</i> 10 g, <i>Ginseng Radix</i> 6 g
		Ma Xing Shi Gan Tang*	<i>Ephedrae Herba</i> 4 g, <i>Gypsum Fibrosum</i> 20 g, <i>Anemarrhenae Rhizoma</i> 9 g, <i>Armeniacae Semen Amarum</i> 10 g, <i>Coicis Semen</i> 10 g, <i>Trichosanthis Fructus</i> 10 g, <i>Rhei Radix et Rhizoma</i> 5 g, <i>Mori Radicis Cortex</i> 10 g, <i>Lepidii seu Descurainiae Semen</i> 6 g, <i>Bubali Cornu</i> 10 g, <i>Pheretima</i> 10 g, <i>Ginseng Radix</i> 6 g
Not reported	Epidemic Toxin Blocking the Lung	Yin Qiao San	<i>Lonicerae Flos</i> 15 g, <i>Forsythiae Fructus</i> 15 g, <i>Schizonepetae Spica</i> 10 g, <i>Menthae Herba</i> 10 g, <i>Arctii Semen</i> 10 g, <i>Platycodonis Radix</i> 10 g, <i>Scutellariae Radix</i> 10 g, <i>Trichosanthis Pericarpium</i> 15 g, <i>Angelicacae Decursivae Radix</i> 15 g, <i>Belamcandae Rhizoma</i> 10 g, <i>Eriobotryae Folium</i> 15 g, <i>Artemisiae Annuae Herba</i> 21 g
		Ma Xing Shi Gan Tang	<i>Ephedrae Herba</i> 5 g, <i>Armeniacae Semen Amarum</i> 10 g, <i>Gypsum Fibrosum</i> 15 g, <i>Scutellariae Radix</i> 10 g, <i>Trichosanthis Pericarpium</i> 15 g, <i>Angelicacae Decursivae Radix</i> 15 g, <i>Belamcandae Rhizoma</i> 10 g, <i>Eriobotryae Folium</i> 15 g, <i>Pumex</i> 20 g, <i>Lepidii seu Descurainiae Semen</i> 10 g, <i>Pheretima</i> 10 g, <i>Artemisiae Annuae Herba</i> 21 g
Not reported	Dampness-Heat Fettering the Lung	Qianjin Weijing Tang + Shangjiao Xuanpi Tang	<i>Phragmitis Rhizoma</i> 15 g, <i>Benincasae Pericarpium</i> 15 g, <i>Coicis Semen</i> 15 g, <i>Armeniacae Semen Amarum</i> 10 g, <i>Scutellariae Radix</i> 10 g, <i>Trichosanthis Pericarpium</i> 15 g, <i>Angelicacae Decursivae Radix</i> 15 g, <i>Belamcandae Rhizoma</i> 10 g, <i>Eriobotryae Folium</i> 15 g, <i>Curcuma longae Radix</i> 15 g, <i>Lepidii seu Descurainiae Semen</i> 10 g, <i>Artemisiae Annuae Herba</i> 21 g
		San Ren Tang	<i>Armeniacae Semen Amarum</i> 10 g, <i>Amomi Fructus Rotundus</i> 5 g, <i>Coicis Semen</i> 15 g, <i>Pinelliae Rhizoma Praeparatum</i> 10 g, <i>Magnoliae Cortex</i> 15 g, <i>Talcum</i> 10 g, <i>Stachyuri Medulla Helwingiae Medulla</i> 5 g, <i>Agastachis Herba</i> 10 g, <i>Poria Sclerotium</i> 15 g, <i>Arecae Pericarpium</i> 15 g, <i>Scutellariae Radix</i> 10 g, <i>Artemisiae Annuae Herba</i> 21 g

* Name of the herbal formula is originally not reported, and the authors named them based on Dictionary of Traditional Chinese Medicine Formula.

△ The compositions of the herbal formula is originally not reported, and the authors added them based on Dictionary of Traditional Chinese Medicine Formula.

the recommendation of *Armeniacae Semen* for the treatment of respiratory diseases in children.

In particular, the frequently used herbs in the recommended herbal formulae for the treatment of pediatric COVID-19 lack diversity compared to the adults [22]. In the recommendations on adult treatment for COVID-19, the herb *Glycyrrhizae Radix et Rhizoma* was the herb with the highest frequency of usage [22]. This might be due to the difference in the spectrum of diseases between the children and the adults. The course of diseases in adults was reported to be more severe than children; thus, the herb *Glycyrrhizae Radix et Rhizoma*, which has both antiviral and anti-inflammatory qualities were highly used. On the other hand, the herb *Armeniacae Semen*, which is widely used of respiratory disease, was highly used as the severity of disease is milder in children.

However, there are several limitations to this study. First, this review only summarized the herbal formulae and their herbal compositions recommended by the traditional medicine guidelines. There was no direct evidence on the efficacy of the herbal formulae for the treatment of pediatric COVID-19. Second, we only found 3 provincial traditional medicine guidelines that included pediatric treatments. This information is insufficient for us to provide any specific recommendations or guidance for the treatment of pediatric COVID-19. Third, this review only summarized information from the provincial traditional medicine guidelines available up to March 25, 2020. As guidelines issued on the pandemic COVID-19 are constantly updated, there may be updated

information that we failed to retrieve in this review.

In conclusion, this review can only be used as a reference for the traditional medicine treatment of pediatric COVID-19. As the spectrum of disease in children differs from adults, there are many questions that remain unanswered. It is important to define the epidemiology of pediatric COVID-19 with more studies.

Author contributions

Conceptualization: MSL and HWL. Methodology: LA and AK. Data Curation: HWL and AK. Writing – Original Draft: LA and HWL. Writing – Review & Editing: JZ, AK, MSL and JAL. Supervision: MSL.

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Ethical statement

No ethics committee approval was required as no human or animal research was conducted.

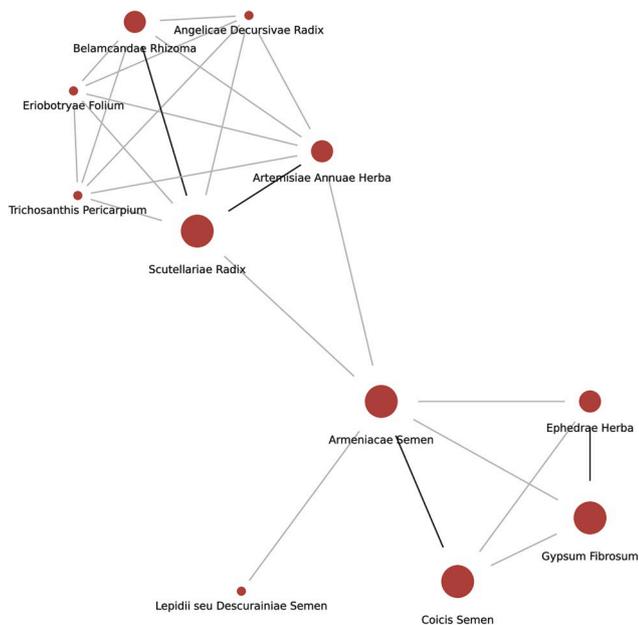


Fig. 1. Network analysis of herbs with frequency of use of 3 or more times.

Data availability

Data will be made available upon request.

Declaration of competing interest

The authors declare no conflict of interest.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctcp.2020.101174>.

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